

REMARKS

Claims 1-106 and 108-109 are canceled, and claims 107, 111 and 112 have been amended. Claims 107 and 110-119 are now pending for the Examiner's consideration.

Claim 107 has been amended to incorporate the limitation of canceled claim 109. Claim 111 has been amended to be written in independent form. Claim 112 has been amended to correct claim dependency. No new matter is added.

Applicant respectfully requests favorable consideration of the pending claims.

1. Claims 107-119 were rejected under 35 U.S.C. § 102(b) as being anticipated by International Application Publication WO 01/37820 ("Shenoy '820"), for the reasons set forth on pages 3-4 of the Office Action. The Examiner argues that Shenoy '820 discloses the malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide in a formulation having the instantly claimed ranges. Applicant believes both of these conclusions are mistaken, and for the reasons that follow, Applicant respectfully traverses.

A. Shenoy '820 Does Not Fairly Disclose the L-Malate Salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide

The Examiner points to a number of passages in Shenoy '820. Applicant has carefully reviewed the passages cited by the Examiner, and is unable to locate a specific disclosure of the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide. Applicant notes that several of the passages cited relate to specific compounds but are not 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide in any form. For example, the eight compounds on cited page 14, lines 4-5 and the single compound on cited page 29, line 5, are chemically different species. The only specific disclosure of the compound 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide is found on page 39, compound 80, and the corresponding synthesis example on page 158, line 28 to page 159, line 8, but these passages show only the free base compound, not the malate salt.

The Shenoy '820 publication does not specifically disclose any salts of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, much less the L-malate salt. Shenoy '820 includes general language around "pharmaceutically acceptable salts" but includes only the following disclosure related to malic acid:

Page 65, lines 1-6:

The term "acid solution" as used herein refers to an acidic solution, typically one which has a pH lower than 7 and is capable of reacting with a basic solution. Preferably the acid in the acid solution is selected from the group consisting of hydrochloric acid, sulfuric acid, formic acid, lactic acid, malic acid, succinic acid, acetic acid, methane sulfonic acid, benzene sulfonic acid, phosphoric acid, and the like, and suitable combinations of two or more hereof.

Page 76, lines 1-4:

In a preferred embodiment of the method of preparing a formulation, the acid solution is selected from the group consisting of hydrochloric acid, sulfuric acid, formic acid, lactic acid, malic acid, and the like, and suitable combinations of two or more hereof, and the base solution is selected from the group consisting of sodium

Page 79, line 30 to page 80, line 2:

suitable combinations of two or more hereof, and the acid solution is selected from the group consisting of hydrochloric acid, sulfuric acid, formic acid, lactic acid, malic acid, succinic acid, acetic acid, methane sulfonic acid, benzene sulfonic acid, phosphoric acid, and the like, and suitable combinations of two or more hereof.

Page 87, lines 8-12:

Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

Claim 11:

11. The formulation of claim 9, wherein said acid solution is selected from the group consisting of hydrochloric acid, sulfuric acid, formic acid, lactic acid, malic acid, succinic acid, acetic acid, methane sulfonic acid, benzene sulfonic acid, and phosphoric acid.

Applicant notes that Shenoy '820 discloses approximately 250 chemical compounds, and each of the cited passages recite numerous acids or salts, but does not specifically associate any of these salts with any particular compound. One would need to select the specific compound, 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, among the hundreds disclosed, and in combination with the specific salt, also listed among many, in order for the reference to provide a fair disclosure of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate. The mere disclosure of a list of salts along with several hundred chemical compounds is not sufficient to be an anticipatory disclosure of each and every combination of compound and salt made possible by the complete set of permutations. Thus, Applicant respectfully suggests that Shenoy '820 does not fairly disclose the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide.

B. Shenoy '820 Does Not Fairly Disclose the Claimed Amounts

Shenoy '820 discloses various ranges for the formulation components. In particular, Shenoy '820 discloses ranges of the active ingredient of 0.01-10%, 0.01-7.5% and 0.01-5% (see, e.g., page 92); and 5-90%, 10-80% and 15-75% (see, e.g., page 96). Shenoy further discloses a particular example having an active ingredient in an amount of 28% (see page 233). Other ranges are described in oil-based formulations (see, e.g., page 98). Applicant respectfully suggests that the ranges and specific amounts presently claimed are not disclosed in Shenoy '820 with sufficient specificity to anticipate the present claims.

It is well settled that a broad range does not anticipate a specific amount, or a specific smaller range, that is within the broad range, unless the claimed amounts or ranges are disclosed in the prior art with "sufficient specificity". MPEP §2131.03. The broad ranges disclosed in Shenoy '820 do not fairly disclose the claimed ranges of active ingredient of 35-

45% (claim 107) and 10-16% (claim 111), much less the specific amounts of 40% (claims 110 and 118) and 15.2% (claims 112 and 119). Further, as shown in the present specification, a formulation having 75% by weight of the malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide results in a composition having undesirable sticking problems in the manufacturing process (see Comparative Example, page 95) whereas the corresponding 40% formulation does not exhibit the sticking problems. The superior processability resulting from compositions within the present narrowly claimed ranges demonstrates that the narrow range is not disclosed in Shenoy '820 with sufficient specificity to be anticipatory.

Applicant respectfully suggests that Shenoy '820 does not provide a fair disclosure of either the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, or of compositions having the present narrowly claimed ranges. Applicant further suggests that Shenoy '820 clearly does not disclose the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide further *in specific combination with* the present narrowly claimed ranges. In fact, only a single compound is exemplified in formulations of Shenoy '820. In order to anticipate the present claims using the Shenoy '820 disclosure, one would have to select a single, non-preferred compound from among several hundred, select a particular salt from among many, and further select specific, narrow ranges of the concentration of the selected salt of the selected compound. Based on the disclosure of Shenoy '820, Applicant does not believe one skilled in the art could "clearly envisage" the presently claimed composition.

Accordingly, Applicant respectfully requests that the rejection of claims 107-119 under 102(b) be withdrawn.

2. Claim 117 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Shenoy '820 in view of U.S. Patent Application Publication No. 2003/0069298 ("Hawley '298"), for the reasons set forth on pages 6-8 of the Office Action. Applicant respectfully traverses.

The Hawley '298 publication is available as 103(a) prior art only under § 102(e). However, the subject matter of the Hawley '298 publication and the claimed invention were, at the time the claimed invention was made, owned by the same person (Pharmacia). Thus, under 35 U.S.C. § 103(c), the Hawley '298 publication is disqualified as 103(a) prior art, and Applicant respectfully requests that the rejection be withdrawn.

Applicant believes all claims are now in condition for allowance. Should there be any issues that have not been addressed to the Examiners satisfaction, Applicant invites the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, including the fee for any required extension of time (for which Applicant hereby petitions), please charge such fees to Deposit Account No. 161445.

Respectfully submitted,

Date: February 1, 2007

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